Systematic review protocol

Exposure to neuroactive non-organochlorine insecticides, and diabetes mellitus and related metabolic disturbances: Protocol for a systematic review and meta-analysis

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Running head: Insecticides, diabetes mellitus and related metabolic disturbances
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Protocol registration and changes

This publication is an update of a protocol first registered in the International Prospective Register of Systematic Reviews (PROSPERO) on June 9 2017 and updated on XX XX 2018 (registration number CRD42017068861, http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017068861). All elements of the protocol have been adjusted to adhere with best practices for systematic reviews. Apart from preliminary searches in scientific databases to assist in the design of search strings, no work on the systematic review was performed before the protocol was changed.

Commented [1]: The PROSPERO registration will be updated in accordance with this manuscript, once the manuscript is approved.

Abstract

Title

Exposure to neuroactive non-organochlorine insecticides, and diabetes mellitus and related metabolic disturbances: Protocol for a systematic review and meta-analysis

Objectives

To assess whether exposure to specific classes of neuroactive non-organochlorine insecticides at levels too low to cause acute intoxication is associated with diabetes mellitus or related metabolic traits.

Methods

Eligibility criteria

Any type of epidemiological and human exposure studies providing an exposure contrast to neuroactive non-organochlorine insecticides and a measure of association to diabetes mellitus or related metabolic traits. We will include published peer-reviewed studies in both English and non-English language.

Information sources

Articles will be located in the NCBI PubMed, Embase, Scopus, Web of Science and LILACS databases, supplemented with manual searching of reference lists and articles citing the included studies.

Risk of bias assessment

Risk of bias in individual studies will be assessed using tools from the Navigation Guide systematic review methodology, while the risk of bias at the outcome level will be assessed according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines.

Data synthesis and analysis

When studies are sufficiently similar in population, exposure, comparator and effect estimate to meaningfully allow quantitative synthesis, we will perform meta-analysis. Otherwise, results will be summarized qualitatively.

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Registration

PROSPERO CRD42017068861.

1 Background

Diabetes mellitus is a heterogeneous group of diseases characterized by varying degrees of insulin insensitivity, decreased insulin production and hyperglycaemia.[1] The global prevalence of diabetes mellitus has been rapidly increasing over the last decades, reaching 8.5% in 2014,[2] and it is estimated that 3.7 million people die annually as a consequence of diabetes mellitus or higher-than-optimal blood glucose.[2] Epidemiological studies have suggested a link between exposure to some pesticides and development of diabetes mellitus,[3-6] which is worrying in the light of the widespread use of pesticides – the annual global consumption of pesticides is estimated at 2.6 billion kilograms, 0.48 billion of which are insecticides.[7] A recent systematic review and meta-analysis by Evangelou *et al* found a summary OR of 1.58 (95% confidence interval 1.32-1.90) for diabetes mellitus when comparing top vs. bottom tertiles of any pesticide exposure.[8]

1.1 Rationale

Higher-than-optimal blood glucose and diabetes mellitus can be considered part of a pathophysiological spectrum rather than separate entities, and higher-than-optimal blood glucose levels below the diagnostic limits for diabetes are responsible for 2.2 million deaths annually.[2] The recent systematic review by Evangelou *et al* on the association between pesticides and diabetes mellitus[8] did not include studies on diabetes-associated metabolic traits. We believe that a new systematic review can add more knowledge to the evidence on the possible association between neuroactive non-organochlorine insecticides and diabetes by also including studies on impaired fasting glucose, glucose intolerance, insulin insensitivity, decreased insulin production and hyperglycaemia below the diagnostic limits for diabetes mellitus.

The majority of the studies included by Evangelou *et al*[8] investigated organochlorine insecticides such as dichloro-diphenyl-trichloroethane (DDT). Pesticides are a heterogeneous group of compounds with different target organisms and modes of action,[9] so it is imprudent to extrapolate health effects of one pesticide or class of pesticides to other classes of pesticides. Evangelou *et al*[8] did not include all relevant classes of pesticides in their search string (e.g. it did not include organophosphate and neonicotinoid insecticides that have a 38% combined share of the insecticide market in monetary value[10]), and they also did not include individual pesticide names, even though articles on specific compounds may not include terms such as “pesticide” or “insecticide”. Furthermore, the filter “humans” was used when searching databases for epidemiological studies, which would have excluded articles that were incorrectly indexed. Taken together, this means that important evidence might have been missed.

1.2 Description of the risk factor

Pesticides are compounds used for killing unwanted organisms, and based on their target organisms they can be broadly categorized as insecticides, nematicides, rodenticides, herbicides or fungicides.[9] These broad classes can be further subdivided based on the specific mode of action of individual compounds.[9] Because of the broad definition of the term "pesticide", it encompasses a huge number of chemical substances: in May 2018 the European Union pesticide database alone contained 1,367 different active substances.[11] We judge it of importance to evaluate the specific active substances separately. Because the previous systematic review on pesticides and diabetes was able to assess the neuroactive organochlorine insecticides,[8] we chose to focus on the neuroactive non-organochlorine insecticides that comprise 85% of the global market for insecticides in monetary value.[10] A list of the classes of insecticides to be included can be seen in the section "Types of exposures" below, while individual compounds are listed in online appendix A.

1.3 Description of the outcome

Apart from the morbidity and mortality directly associated with diabetes mellitus, it is a major risk factor for e.g. myocardial infarction, kidney failure, peripheral vascular disease and lower limb amputations.[2] The disease is a continuous spectrum of hyperglycaemia, insulin insensitivity, and decreased insulin production. This is reflected in the changes of diagnostic criteria made by the World Health Organization based on studies showing negative health effects of hyperglycaemia: The 1980 cut-off for fasting plasma glucose was 8.0 mmol/litre,[12] changed to 7.8 mmol/litre[13] in 1985 and to the current value of 7.0 mmol/litre in 1998.[14] Even with the current definition, higher-than-optimal blood glucose values below the diagnostic cut-off are associated with significant morbidity and mortality.[2]

Because of the continuous nature of the disease process, this systematic review will focus on diabetes mellitus as defined by the diagnostic criteria at the time of the individual studies, but also include studies on hyperglycaemia, insulin insensitivity and decreased insulin production.

1.4 How the risk factor may impact the outcome

While physical inactivity, overweight and genetic disposition are important risk factors for diabetes mellitus,[2] chemical exposures can also play a role in its aetiology. It is well known that some drugs interfere with glucose regulation, increasing the risk of diabetes mellitus among predisposed individuals.[1] The glucose analogue streptozotocin is selectively toxic to the insulin-producing beta-cells of the pancreas[15] and is used to create rodent models of diabetes mellitus. The rodenticide Vacor was also toxic to beta cells and lead to a phenotype similar to type 1 diabetes in humans who attempted suicide with the compound.[16]

A complete review of mechanisms that may link diabetes mellitus with exposure to neuroactive non-organochlorine insecticides is out of scope of this protocol, but there are indications of a causal link. Hyperglycaemia has been reported in connection with human acute high-dose intoxication with pyrethroids,[17] organophosphates,[18] carbamates[19] and neonicotinoids[20]. While hyperglycaemia is a part of the acute stress response,[21] and the hyperglycaemia seen in acute high-dose poisoning may be an unspecific marker of physiological stress, a plethora of possible mechanisms by which insecticide exposure might lead to diabetes mellitus and related metabolic disturbances has been suggested. Depending on the specific compound or class of compounds, mechanisms may include changes in lipid metabolism,[22] inflammation,[22] oxidative stress,[22] changes in the gut microbiome,[3] interference with insulin release from the beta cells of the pancreas,[22] or other endocrine-disruptive effects.[23]

2 Objectives

We aim through a systematic review and meta-analysis to assess whether exposure to specific classes of neuroactive non-organochlorine insecticides at levels too low to cause acute intoxication is associated with diabetes mellitus, or related metabolic traits such as prediabetes (impaired fasting glucose or glucose intolerance), hyperglycaemia, or insulin resistance.

3 Methods

The systematic review will be carried out according to the Navigation Guide guidelines for systematic reviews in environmental health[24], and will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[25] This protocol conforms to the PRISMA Protocols (PRISMA-P) guidelines, and its abstract conforms to the PRISMA for Abstracts (PRISMA-A) guidelines.[26] In case any methodological changes from this protocol are made during the review, they will be listed under the heading “Differences between protocol and review” in the final article.

3.1 Eligibility criteria

3.1.1 Types of populations

Any human population.

3.1.2 Types of exposures

Occupational or environmental exposure to neuroactive non-organochlorine insecticides, defined as non-organochlorine insecticidal compounds whose main toxico-dynamic target is the nervous system according to the classification system by the Insecticide Resistance Action Committee.[27] We will not include DDT, its analogues or other organochlorine insecticides, since they have been reviewed recently[8] and furthermore most of these compounds are already severely restricted due to health risk concerns,[28] and currently have a small market share.[10] Nor will we include nicotine, even though it can be categorized as a neuroactive insecticide, because we consider it obsolete as a pesticide, and it is estimated to have no significant market share.[10]

Specifically, the included classes of insecticides are:

- Carbamates
- Organophosphates
- Fiproles
- Pyrethroids and pyrethrins
- Neonicotinoids
- Sulfoximines
- Butenolides
- Spinosyns
- Avermectins and milbemycins
- Pymetrozine
- Flonicamid
- Nereistoxin analogs
- Amitraz
- Oxadiazines
- Semicarbazones
- Diamides

The individual insecticides in these classes can be seen in appendix A.

We will include studies with quantitative measures of exposure, as well as more crude exposure measures (such as professions/industries/work sites), as long as the insecticide used is stated and falls within one of the above-mentioned categories.

3.1.3 Types of comparators

Humans exposed to no or lower levels of neuroactive non-organochlorine insecticides than the more highly exposed population.

3.1.4 Types of outcomes

While the main outcome of interest is diabetes mellitus, we will also include studies on the additional outcomes shown in Table 1 Types of included outcomesTable 1.

Table 1 Types of included outcomes

Condition	Classification in ICD-10*, if applicable	
	Name	**Code**
Diabetes mellitus	Diabetes mellitus	E10-E14
Hyperglycaemia/increased blood glucose levels	Hyperglycaemia, unspecified	R73.9
Impaired fasting glucose	-	-
Glucose intolerance	Abnormal glucose tolerance test	R73.0
Insulin insensitivity	-	-
Decreased insulin production	-	-

* ICD-10 = International Classification of Diseases, 10th Revision.[29]

When the outcome in a study is diabetes mellitus, it must be defined by register data, fasting plasma glucose, oral glucose tolerance test, glycated haemoglobin A (HbA_{1c}), or a combination of at least one of these measures, optionally in combination with patient self-report. We will not include studies where diabetes mellitus is defined only by patient self-report or by measurement of random plasma glucose or glycosuria.

3.1.5 Types of studies

3.1.5.1 Inclusion criteria

Any type of epidemiological (cross-sectional, case-control, cohort, ecological etc.) and human exposure studies providing an exposure contrast to the neuroactive non-organochlorine insecticides listed in appendix A and a measure of association to the outcomes of interest. Studies without a measure of association will be included if they provide enough information to calculate such a measure.

3.1.5.2 Exclusion criteria

- Case reports, case series, animal studies, *ex vivo* studies (including studies on human cells and tissues) and *in silico* studies.
- Studies only considering exposure to “insecticides” or “pesticides” as broad categories, or exposure to a mixture of pesticides that includes compounds that cannot be classified as neuro-active non-organochlorine insecticides.
- Studies without estimates of association (e.g. only reporting prevalence or incidence of diabetes in an insecticide-exposed group, but without a control group).
- Studies on insecticide poisoning requiring acute medical treatment.

3.1.5.3 Years considered

Any year of publication. All searches will be re-run within 12 months of publication of the systematic review. New hits will be screened in the same manner as hits in the original search (see below). When deciding on whether to include new eligible studies in the systematic review, their potential influence on the conclusions of the systematic review will be weighed against the resulting delay in publication. If we choose not to include such new studies, we will provide a comprehensive list of the studies in an appendix.

3.1.5.4 Publication language

We will not exclude any articles based on language, but we will only actively search for articles using English terms (except for the LILACS database, where Spanish, French and Portuguese terms will also be used). Articles in languages other than the ones spoken by the reviewers (Danish, English, German, Norwegian and Spanish) will be translated into English using Google Translate (https://translate.google.com/).

3.1.5.5 Publication status

Peer-reviewed publications.

3.1.6 Types of effect measures

For binary outcomes, we will prioritize relative effects measures such as risk ratio, odds ratio and hazard ratio depending on the study design. Absolute effect measures will be considered if no relative effect measures are available. For continuous outcomes such a fasting plasma glucose, we will include both relative and absolute effect measures.

If results from both unadjusted and adjusted analyses are presented in a study, we will include results from the most adjusted one, unless we suspect over-adjustment (i.e., adjustment for a factor that is on the causal path from exposure to outcome), in which case we may choose a less adjusted model.

Because of the known and strong correlations between e.g. family history, age and diabetes mellitus, we will not be able to convert adjusted odds ratios for diabetes mellitus into relative risks, since the conversion requires an a common "assumed control risk" for all the non-exposed persons.[30] We will only combine adjusted odds ratios and adjusted relative risks in meta-analysis if the prevalence of diabetes mellitus in the studies reporting odds ratios is ≤ 10%, since the odds ratio will then be numerically very similar to the relative risk.[31]

3.2 Information sources and search

Searches will be performed in the following scientific databases:

- NCBI PubMed
- Embase
- Scopus
- Web of Science
- LILACS (http://lilacs.bvsalud.org)

The search terms for each of these 5 databases are included in online appendices B-F.

A hand search for potentially eligible articles will be performed in the reference list of included articles, among the articles that cite any of the included articles, and in the reference lists of existing reviews on the subject. Experts on negative health effects of pesticides will be presented with the list of included studies and will be asked to identify any further eligible studies.

The removal of *in vitro*, *in silico* and animal studies (see eligibility criteria above) will be done manually rather than by the use of search filters because studies might have been erroneously indexed in the article databases.

3.3 Study selection

Two independent reviewers (MRHH and JS) will screen search hits for eligibility first at the title, then at the abstract and finally at the full text level. Conflicts will be solved by consulting a third review author. In the systematic review, a flow-chart of article in- and exclusion will be provided in accordance with the PRISMA[25] guidelines.

3.4 Data extraction and data items

Records and data will be managed using the DistillerSR[32] web application for systematic reviews. Two independent investigators (MRHH and JS) will design and pilot data extraction forms until agreement is achieved, with mediation by a third investigator if agreement cannot be achieved. Data entry will also be extracted by two separate investigators (MRHH and JS), with mediation by a third investigator in case of disagreements.

We will prepare three separate data extraction forms – one for extracting study characteristics, one for assessing risk of bias (see included parameters in the section “Risk of bias assessment”), and one for extracting effect estimates. The forms will be filled out in the order listed (i.e. risk of bias assessment will be done before extraction of effect estimates).

As a minimum, the study characteristics form will include the following information on each primary study:

- First author name
- Year of publication
- Region
- Study design (cross-sectional, case-control, cohort, etc.). Will be assessed by the systematic review authors instead of using labels used by investigators in primary study.
- Participants
    - Exposed population

- Comparators
- Percent participation

- Exposure
  - Type of exposure (environmental or occupational)
  - Assessment method (biomarker, environmental measurements, register or questionnaire)
  - Specific insecticides assessed
- Outcome
  - Type of outcome (diabetes mellitus, insulin insensitivity, fasting blood glucose as continuous measure, etc.). If the outcome is diabetes mellitus, we will record whether it was type 1, type 2 or unspecified (assessed by systematic review authors; we will not rely on labels used by investigators in primary study).
  - Definition of outcome by the study authors.

The form for extracting effect estimates will have separate fields for each identified exposure-outcome pair. Effect estimates will be extracted with their 95% confidence intervals. If no confidence interval is available, but an exact p-value is, we will extract the p-value and calculate a 95% confidence interval.

Any missing data deemed necessary for the systematic review will be requested from the corresponding author of the primary study in question.

3.5 Risk of bias assessment

Risk of bias will be considered both at the outcome and the individual study level. The risk of bias at the outcome level will be assessed as part of the assessment of the quality of evidence (see below). All assessment of risk of bias will be done by two separate investigators with mediation by a third investigator in case of disagreements.

Risk of bias at the individual study level will be assessed according to the Navigation Guide systematic review methodology as illustrated by a previous systematic review on the reproductive toxicity of the biocide triclosan.[33] For each domain in the risk of bias assessment (e.g., "exposure assessment" or "confounding"), the support for judgement (in the form of verbatim quotes from the original articles and/or comments from the systematic review authors) will be provided as suggested by the Cochrane Handbook.[34] In the domain "Conflict of interest", we will include author financial conflicts of interest and study funding from the agrochemical, agricultural or food industries. Both disclosed and undisclosed conflicts will be included as described in a systematic review by Mandrioli *et al*.[35]

3.6 Assessing quality of evidence

The quality of evidence at the level of each exposure-outcome pair will be graded according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines[36], adapted to the setting of occupational medicine.[37] We will include an assessment of the risk of meta-biases due to publication bias and selective reporting. Risk of publication bias will be assessed qualitatively if we identify 9 studies or less for an exposure-outcome pair, while we will use funnel plots if we identify at least 10 studies. To assess the risk of bias due to selective reporting, we will attempt to locate published protocols of included studies.

3.7 Summary measures and synthesis of results

For each exposure-outcome pair where we include two or more studies, we will qualitatively assess whether the studies are sufficiently similar in exposed population, comparator and type of effect estimate to allow quantitative synthesis in a meaningful manner. E.g., studies on environmentally and occupationally exposed persons will not be combined quantitatively, unless biomarkers show that exposure levels are comparable. This assessment will be done by two separate investigators, with mediation by a third investigator in case of disagreements. If quantitative synthesis is deemed inappropriate, we will synthesize the results qualitatively based on their consistency. If we deem that at least two studies are sufficiently similar for quantitative analysis, we will test for study heterogeneity using the I^2 statistic.[31] If no significant heterogeneity is identified, results will be synthesized in a meta-analysis using the inverse variance method with a random effects model.[31] Adjusted and unadjusted effect estimates will not be combined quantitatively. The summary measures will depend on the effect measures reported in the individual studies. E.g., if articles report odds ratios, we will calculate meta-odds ratios, and if articles report regression coefficients from linear regression models on blood glucose values, we will calculate meta-coefficients.

3.8 Additional analyses

To assess the impact (direction and size) of the risk of bias in individual studies, we will repeat any quantitative synthesis of results for each exposure-outcome pair, stratified by overall risk of bias (low risk or probably low risk vs. probably high risk, high risk or unclear risk) provided that each stratum contains at least two studies. If the strata contain less than two studies each, we will qualitatively assess the impact of the risk of bias.

Since *in silico*, *in vitro* and animal studies will not be included in the systematic review, we will refrain from speculating on the possible mechanistic links between exposure to neuroactive non-organochlorine insecticides and disruption of glucose homeostasis. Also, since we will not review the benefits of using these compounds (e.g., in agriculture and public health programs targeted against malaria) in this systematic review, we will give no recommendations regarding their use.

3.9 Data sharing

The DistillerSR database used in the systematic review will be exported and included in the final publication as an online supplement to ensure complete transparency.

4 Financial support

The development of this protocol was not supported by any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. We will not apply for any funding for the systematic review, apart from as needed to pay open access publication fees.

5 Conflicts of interest

The authors declare that they have no conflicts of interest in relation to the subject of the systematic review.

6 Author contributions

MRHH and VS contrived the systematic review. MRHH and VS gathered the review team. MRHH and VS lead and all authors contributed to the development of the protocol. MRHH and JS are the lead reviewers of this systematic review. MRHH wrote the first draft of this protocol and EJ, AS, HAK, JS and VS made substantial contributions to the designs of the systematic review and to revisions of the manuscript. MRHH is the guarantor of the systematic review.

7 Acknowledgements

The opinions expressed in this article are the responsibility of the authors alone and do not necessarily reflect the policies of their respective institutions.

8 References

1 American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2010;33:S62-S69.
2 Global report on diabetes. World Health Organization, Geneva, 2016.
3 Velmurugan G, Ramprasath T, Swaminathan K et al. Gut microbial degradation of organophosphate insecticides-induces glucose intolerance via gluconeogenesis. Genome Biol 2017;18:8.
4 Wang J, Zhu Y, Cai X, Yu J, Yang X, Cheng J. Abnormal glucose regulation in pyrethroid pesticide factory workers. Chemosphere 2011;82:1080-1082.
5 Saldana TM, Basso O, Hoppin JA et al. Pesticide exposure and self-reported gestational diabetes mellitus in the Agricultural Health Study. Diabetes Care 2007;30:529-34.
6 Montgomery MP, Kamel F, Saldana TM, Alavanja MC, Sandler DP. Incident diabetes and pesticide exposure among licensed pesticide applicators: Agricultural Health Study, 1993-2003. Am J Epidemiol 2008;167:1235-46.
7 Atwood D, Paisley-Jones C. Pesticides industry sales and usage 2008–2012 market estimates. US Environmental Protection Agency, Washington, DC.
8 Evangelou E, Ntritsos G, Chondrogiorgi M et al. Exposure to pesticides and diabetes: A systematic review and meta-analysis. Environ Int 2016;91:60-8.
9 Casida JE. Pest toxicology: the primary mechanisms of pesticide action. Chem Res Toxicol 2009;22:609-19.
10 Sparks TC, Nauen R. IRAC: Mode of action classification and insecticide resistance management. Pesticide Biochemistry and Physiology 2015;121:122-128.
11 European Commision: EU Pesticides database. 2018, http://ec.europa.eu/food/plant/pesticides/eu-pesticides-database (accessed 25 May 2018).
12 WHO Expert Committee on Diabetes Mellitus. Second Report. Technical Report Series 646. World Health Organization, Geneva, 1980.
13 Diabetes Mellitus: Report of a WHO Study Group. Technical Report Series 727. World Health Organization, Geneva, 1985.
14 Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998;15:539-53.
15 Lenzen S. The mechanisms of alloxan- and streptozotocin-induced diabetes. Diabetologia 2008;51:216-26.
16 Karam JH, Lewitt PA, Young CW et al. Insulinopenic diabetes after rodenticide (Vacor) ingestion: a unique model of acquired diabetes in man. Diabetes 1980;29:971-8.
17 Kim D, Moon J, Chun B. The initial hyperglycemia in acute type II pyrethroid poisoning. J Korean Med Sci 2015;30:365-70.
18 Moon JM, Chun BJ, Cho YS. Hyperglycemia at presentation is associated with in hospital mortality in non-diabetic patient with organophosphate poisoning. Clin Toxicol (Phila) 2016;54:252-8.
19 Satar S, Satar S, Sebe A, Yesilagac H. Carbofuran poisoning among farm workers. Mt Sinai J Med 2005;72:389-92.
20 Todani M, Kaneko T, Hayashida H et al. [Acute poisoning with neonicotinoid insecticide acetamiprid]. Chudoku Kenkyu 2008;21:387-90.
21 Marik PE, Bellomo R. Stress hyperglycemia: an essential survival response! Critical Care 2013;17:305-305.
22 Lasram MM, Dhouib IB, Annabi A, El Fazaa S, Gharbi N. A review on the molecular mechanisms involved in insulin resistance induced by organophosphorus pesticides. Toxicology 2014;322:1-13.
23 Xiao X, Clark JM, Park Y. Potential contribution of insecticide exposure and development of obesity and type 2 diabetes. Food Chem Toxicol 2017;105:456-474.

24 Woodruff TJ, Sutton P. An evidence-based medicine methodology to bridge the gap between clinical and environmental health sciences. Health Aff (Millwood) 2011;30:931-7.

25 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264-9, w64.

26 Beller EM, Glasziou PP, Altman DG et al. PRISMA for Abstracts: Reporting Systematic Reviews in Journal and Conference Abstracts. PLOS Medicine 2013;10:e1001419.

27 IRAC International MoA Working Group. IRAC Mode of Action Classification Scheme 8.3: IRAC Resistance Action Committee 2017, http://www.irac-online.org/documents/moa-classification/?ext=pdf (accessed 25 May 2018).

28 Stockholm Convention on Persistent Organic Pollutants (POPs) as amended in 2009: Stockholm Convention 2010.

29 ICD-10: International Statistical Classification of Diseases and Related Health Problems: 10th Revision. World Health Organization, Geneva, 2015.

30 O'Connor AM. Interpretation of odds and risk ratios. J Vet Intern Med 2013;27:600-3.

31 Sterne J, Kirkwood B. Essential Medical Statistics. Hoboken, NJ, USA: Wiley-Blackwell, 2010.

32 DistillerSR. Ottawa, Canada: Evidence Partners. https://www.evidencepartners.com/products/distillersr-systematic-review-software/ (accessed 25 May 2018).

33 Johnson PI, Koustas E, Vesterinen HM et al. Application of the Navigation Guide systematic review methodology to the evidence for developmental and reproductive toxicity of triclosan. Environ Int 2016;92-93:716-28.

34 Deeks J, Higgins J, Altman D, Green S. Cochrane handbook for systematic reviews of interventions version 5.1. 0 (updated March 2011). The Cochrane Collaboration 2011.

35 Mandrioli D, Kearns CE, Bero LA. Relationship between Research Outcomes and Risk of Bias, Study Sponsorship, and Author Financial Conflicts of Interest in Reviews of the Effects of Artificially Sweetened Beverages on Weight Outcomes: A Systematic Review of Reviews. PLoS One 2016;11:e0162198.

36 Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is "quality of evidence" and why is it important to clinicians? Bmj 2008;336:995-8.

37 Morgan RL, Thayer KA, Bero L et al. GRADE: Assessing the quality of evidence in environmental and occupational health. Environ Int 2016;92-93:611-6.

38 The WHO recommended classification of pesticides by hazard and guidelines to classification 2009. World Health Organization, Geneva, 2009.

Appendix A: List of insecticides to be considered in the systematic review

- Carbamates: Alanycarb, aldicarb, aminocarb, bendiocarb, benfuracarb, butocarboxim, butoxycarboxim, carbaryl, carbofuran, carbosulfan, ethiofencarb, fenobucarb, fenothiocarb, fenoxycarb, formetanate, furathiocarb, isolan, isoprocarb, methiocarb, methomyl, metolcarb, oxamyl, pirimicarb, propoxur, thiodicarb, thiofanox, triazamate,trimethacarb, XMC, xylylcarb
- Organophosphates: Acephate, amiton, azamethiphos, azinphos-ethyl, azinphosmethyl, cadusafos, chlorethoxyfos, chlorfenvinphos, chlormephos, chlorpyrifos, chlorpyrifos-methyl, coumaphos, crufomate, cyanophos, cyanofenphos, cythioate, demeton-S-methyl, diazinon, dichlorvos/DDVP, dicrotophos, dimethoate, dimethylvinphos, disulfoton, EPN, ethion, ethoprophos, etrimfos, famphur, fenamiphos, fenitrothion, fenthion, fonofos, formothion, fosthiazate, fensulfothion, heptenophos, imicyafos, isofenphos, isopropyl O-(methoxyaminothio-phosphoryl) salicylate, isoxathion, leptophos, malaoxon, malathion, mecarbam, methacrifos, methamidophos, methidathion, mevinphos, mipafox, monocrotophos, naled, omethoate, oxydemeton-methyl, parathion, parathion-methyl, phenthoate, phorate, phosalone, phosmet, phosphamidon, phoxim, pirimiphos-methyl, profenofos, propetamphos, prothiofos, pyraclofos, pyridaphenthion, quinalphos, sulfotep, tebupirimfos, temephos, terbufos, tetrachlorvinphos, thiometon, triazophos, tributyl phosphorotrithioite, trichlorfon, vamidothion
- Fiproles: Ethiprole, fipronil
- Pyrethroids and pyrethrins: Acrinathrin, allethrin, bifenthrin, bioallethrin, bioresmethrin, cycloprothrin, cyfluthrin, cismethrin, cyhalothrin, cypermethrin, cyphenothrin, deltamethrin, empenthrin, esfenvalerate, etofenprox, fenpropathrin, fenvalerate, flucythrinate, flumethrin, *tau*-fluvalinate, halfenprox, imiprothrin, kadethrin, permethrin, phenothrin, prallethrin, pyrethrum, resmethrin, silafluofen, tefluthrin, tetramethrin, tralomethrin, transfluthrin
- Neonicotinoids: Acetamiprid, clothianidin, dinotefuran, imidacloprid, nitenpyram, nithiazine, thiacloprid, thiamethoxam
- Sulfoximines: Sulfoxaflor
- Butenolides: Flupyradifurone
- Mesoionics: Triflumezopyrim
- Spinosyns: Spinetoram, spinosad
- Avermectins and milbemycins: Abamectin, emamectin benzoate, lepimectin, milbemectin
- Pyridine azomethine derivatives: Pymetrozine, pyrifluquinazon

- Flonicamid
- Nereistoxin analogs: Bensultap, cartap hydrochloride, thiocyclam, thiosultap-sodium
- Amitraz
- Oxadiazines: Indoxacarb
- Semicarbazones: Metaflumizone
- Diamides: Chlorantraniliprole, cyantraniliprole, flubendiamide

List of classes of insecticides compiled from the IRAC Mode of Action Classification Scheme.[27] Individual pesticide names extracted from the same publication, supplemented with the WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification 2009[38] and (for the classes of carbamates, neonicotinoids, pyrethroids and organophosphates) Embase Emtree.

If additional compounds belonging to the above-mentioned classes of insecticides are identified during the review process, we may include them as well.